REMARKS

Claims 1-86 were pending in the present application and claims 13-86 have been withdrawn from consideration. By the amendment submitted herewith, claims 1-4, 6-7, 9-11 and 13-86 are canceled without prejudice to the prosecution of the encompassed subject matter in any related continuation, continuation-in-part or divisional application, claims 5 and 8 are amended and new claims 87-90 are added to particularly point out and distinctly claim certain embodiments encompassed by the invention.

Support for the present amendments may be found in the application as originally filed, for example, in the specification at page 12, lines 6-29; page 24, lines 25-30; page 27, line 14 through page 29, line 9; page 29, lines 19-22; page 31, line 21 through page 32, line 14; page 34, line 24 through page 35, line 3, page 36, line 31 through page 37, line 15; page 54, lines 3-11; page 55, line 18 through page 56, line 3, page 60, lines 20-33; page 61, line 21 through page 62, line 31; page 64, lines 8-15; and elsewhere. No new matter is introduced by way of the present amendment.

The present amendment is submitted further to the Notice of Non-Compliant Amendment mailed by the PTO on January 10, 2008, further to applicants' submissions of October 29, 2007, and July 26, 2007. The PTO asserts that in the submissions of July 26, 2007, and October 29, 2007, canceled claims 13-86 were not compliant with 37 C.F.R. §1.121(c)(4)(i), which states that no claim text shall be presented for any claim in the claim listing with the status of 'canceled'. Applicants' undersigned representative believes that any non-compliance with the cited rule was the result of an inadvertent computer-generated typographical error incident to the electronic submissions made to the PTO on July 26, 2007, and October 29, 2007, by which a portion of the text of canceled claim 13 was unintentionally retained, and submits that as presented herewith the amendment fully complies with the provisions of 37 C.F.R. §1.121. Reconsideration of the corrected amendment and the present Remarks, in which the aforementioned typographical error in claim 13 has been corrected and which is otherwise the same as the submission made on October 29, 2007, are therefore respectfully requested.

CLAIM OBJECTIONS

The PTO objects to an informality in claim 5, asserting that a sequence identifier and a Sequence Listing entry are required for the amino acid sequence recited in this claim. As presently amended, claim 5 recites "SEQ ID NO:26", which sequence is disclosed in the application as originally filed (*e.g.*, in the specification at page 29, lines 19-22) and is included in the sequence amendment that was submitted to the PTO on April 18, 2005, as reflected in the Sequence Listing that appears in the application as published by the PTO on October 6, 2005. Accordingly, the objection has been overcome and its withdrawal is respectfully requested.

REJECTIONS UNDER 35 U.S.C. §101

The PTO rejects claims 1-12 under 35 U.S.C. §101, as allegedly drawn to non-statutory subject matter. In particular, the PTO asserts that the present wording of the claims encompasses naturally-occurring polypeptides and compositions, which are not the products of human activity.

Applicants respectfully traverse this ground for rejection and submit that the present application as amended herewith is directed to statutory subject matter. The instant embodiments are directed to a composition for maintaining pluripotency without differentiating a stem cell, comprising an isolated polypeptide having a WIF domain and an EGF-like repeat; and an isolated stem cell survival agent that is selected from stem cell factor (SCF), Flt-3 ligand (FL) and thrombopoietin (TPO), wherein the polypeptide having said WIF domain comprises a polypeptide selected from (a) a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO:4, (b) a WIF domain polypeptide consisting of a sequence of at least 100, 110, 120, 130, 140 or 150 amino acids of the amino acid sequence set forth in SEQ ID NO:4, wherein said WIF domain polypeptide is capable of maintaining pluripotency of a stem cell without differentiating the stem cell, (c) a WIF domain polypeptide comprising an amino acid sequence that is derived from the amino acid sequence set forth in SEQ ID NO:4 by substitution, deletion or addition of 1 to 10 amino acids therein, wherein said WIF domain polypeptide is capable of maintaining pluripotency of a stem cell without differentiating the stem cell, and (d) a WIF

domain polypeptide comprising an amino acid sequence that is derived from the polypeptide of (b) by substitution, deletion or addition of 1 to 10 amino acids therein, wherein said WIF domain polypeptide is capable of maintaining pluripotency of a stem cell without differentiating the stem cell.

As a first matter, the cancellation without prejudice of claims 1-4, 6-7 and 9-11 by amendment renders moot the rejections of these claims. Additionally, claim 8 (from which claims 5 and 12 depend) as amended relates in pertinent part to an *isolated* polypeptide, and as such is clearly directed to statutory subject matter. Support for what is meant by "isolated" can be found in the specification, for example, at page 24, lines 25-30. Accordingly, it is respectfully submitted that the rejection under §101 has been overcome, such that its withdrawal is requested.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The PTO rejects claims 1-5, 7-9, 11 and 12 under 35 U.S.C. §112, first paragraph, as allegedly failing to satisfy the written description requirement. Specifically, the Examiner asserts that a WIF domain "encompasses essentially unlimited variants of the 'WIF domain' found in WIF-1 polypeptides", asserting further that according to claim 2, a WIF domain-containing polypeptide may have "as little as 3% sequence identity with naturally occurring WIF domains." With regard to claim 11, the PTO asserts that the three disclosed species of "stem cell survival agent" are not sufficient to describe a broad genus encompassing any agent that is essential for survival of any stem cell, alleging further that functionally defining such an agent—without structurally defining the genus--falls short of meeting the written description requirement.

Applicants respectfully traverse these grounds for rejection and submit that the present application satisfies the requirements of 35 U.S.C. §112, first paragraph, including the written description requirement. The instant embodiments are directed in pertinent part to a composition for maintaining pluripotency without differentiating a stem cell, comprising an isolated polypeptide having a WIF domain and an EGF-like repeat; and an isolated stem cell survival agent, as noted above. As also noted above, the cancellation without prejudice of claims 1-4, 7, 9 and 11 by amendment renders moot the rejections of these claims.

Specifically, it is submitted that the present application clearly conveys that at the time of filing, applicants were in possession of a composition comprising (i) an isolated WIF domain-containing polypeptide having an EGF-like repeat and (ii) an isolated stem cell survival agent selected from stem cell factor (SCF), Flt-3 ligand (FL) and thrombopoietin (TPO).

With regard to (i) an isolated WIF domain polypeptide, as disclosed in the specification and recited in the claims, it is readily apparent that the application unambiguously provides such polypeptides. Throughout the application there can be found numerous references to, *inter alia*, a polypeptide comprising (a) the amino acid sequence set forth in SEQ ID NO:4, as set forth in original claim 10 and in the Sequence Listing, and as described for use in the presently claimed embodiments in the specification, for instance, at page 9, lines 8-16; page 27, line 14 through page 29, line 9; Figure 1; and elsewhere. There and elsewhere the specification also clearly conveys to the skilled person that at the time of filing applicants were in possession of (b) a WIF domain polypeptide, in particular by teaching that a WIF domain refers to the N-terminal region of the WIF-1 protein (*e.g.*, SEQ ID NOS:2, 4, 8, 10) without the signal peptide and extending to the start of the EGF-like repeat (*e.g.*, page 29, line 11 through page 30, line 9), and further by explaining that the WIF domain includes the amino acid sequences running from about position 30 to about position 180 in these SEQ ID NOS, beyond which the presence of an EGF-like repeat-containing domain can be readily recognized, as also clearly described.

The specification also clearly describes smaller WIF domain-containing polypeptides, such as those that include at least 100, 110, 120, 130, 140 or 150 amino acids of the amino acid sequence at about position 30 to about position 180 in SEQ ID NO:4 (*e.g.*, page 29, lines 1-4). The application teaches further how to confirm the function of such a WIF domain polypeptide, *e.g.*, that it is capable of maintaining pluripotency of a stem cell without differentiating the stem cell, for instance, by teaching at page 28, lines 8-13, that a functional WIF domain may be identified using an *in vitro* Wnt protein inhibition assay according to art-accepted methodology.

Based on the teachings of the present application in view of well known methodologies in the art, applicants also submit that in the specification there is more than adequate description to show possession of a WIF domain polypeptide comprising an amino acid

sequence that is derived from the amino acid sequence set forth in SEQ ID NO:4 (*e.g.*, claim 8, part (c)) or from a WIF domain polypeptide of 100-150 amino acids of the amino acid sequence at about position 30 to about position 180 in SEQ ID NO:4 (*e.g.*, page 28, line 13 through page 29, line 9; *see* claim 8, part (b)), by substitution, deletion or addition of 1 to 10 amino acids therein, as disclosed, for example at page 36, line 31 through page 37, line 15. From Example 8 (pages 97-100), which describes how similar conservatively substituted derivatives of SEQ ID NO:2 were made and tested to show that the so-modified WIF domain polypeptide was capable of maintaining pluripotency of a stem cell without differentiating the stem cell, it is submitted that possession of the subject matter encompassed by the instant claims is unquestionably within the teachings of the present application, given the state of the art.

Additionally, applicants submit that clear description of structural and functional attributes of an EGF-like repeat is provided by the specification, with regard to the presently recited isolated WIF domain-containing polypeptide having such an EGF-like repeat, for instance, at page 29, line 11 through page 30, line 9; and at page 55, line 9 through page 56, line 3. It is therefore to be noted that the differentiation regulation activity of the EGF-like repeat in the WIF polypeptide is expressly contemplated, in particular where the activity of maintaining stem cell pluripotency without differentiating the stem cell is for the first time disclosed in the present application (*see also, e.g.,* Examples 4-5).

Furthermore, applicants respectfully traverse the PTO's assertion with regard to "stem cell survival agent" and submit that there is no written description deficiency in the present application with respect to this element. Nevertheless, without acquiescence in any rejection and solely for purposes of advancing prosecution of the present application, claim 11 has been canceled without prejudice by amendment herewith. As presently disclosed in the specification (*e.g.*, at page 31, line 21 through page 32, line 14) and as recited in the amended claims, the present embodiments contemplate an isolated stem cell survival agent that may be stem cell factor (SCF), Flt-3 ligand (FL) or thrombopoietin (TPO), all of which are stem cell survival agents disclosed in a manner that conveys relevant identifying characteristics and all of which are known to the art. That which is already known in the art need not be described again in the specification (*Capon v. Eshhar*, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005)).

Accordingly and in view of the foregoing, it is submitted that the present application satisfies the requirements of 35 U.S.C. §112, first paragraph, such that withdrawal of the rejections is respectfully requested.

REJECTIONS UNDER 35 U.S.C. §102

The PTO rejects claims 1-10 under 35 U.S.C. §102 for alleged lack of novelty over Hsieh et al. (1999 *Nature* 398:431-436, of record). Specifically, the PTO asserts that Hsieh et al. teach a polypeptide having an amino acid sequence identical to that set forth in SEQ ID NO:4 of the present application, asserting further that the polypeptide of Hsieh et al. would be assumed inherently to possess the presently recited functional properties.

Applicants respectfully traverse these grounds for rejection. The presently claimed embodiments are directed in pertinent part to a composition for maintaining pluripotency without differentiating a stem cell, comprising an isolated polypeptide having a WIF domain and an EGF-like repeat; and an isolated stem cell survival agent that is selected from stem cell factor (SCF), Flt-3 ligand (FL) and thrombopoietin (TPO). As also noted above, the cancellation without prejudice of claims 1-4, 6-7 and 9-10 by the present amendment renders moot the rejections of these claims.

It is axiomatic that for the PTO to establish a *prima facie* case of anticipation under 35 U.S.C. §102, each and every element of the claimed combination must be disclosed as such in the single cited document. As conceded by the PTO in the Action at page 11, lines 13-14, "Hsieh et al. does not teach that the composition comprises a stem cell survival agent." Applicants therefore submit that the PTO fails to establish a case of anticipation over the instant claims because Hsieh et al. fail to teach (or even remotely suggest) the presently recited composition, in particular where Hsieh et al. fail in any way to contemplate the combination of (i) an isolated WIF domain/EGF-like repeat polypeptide *and* (ii) an isolated stem cell survival agent that is selected from SCF, FL and TPO.

In this regard, Hsieh et al. merely describe the effects of WIF-1 overexpression on somitogenesis and development of paraxial presomitic mesoderm, notochord, brachial arches and neural crest derivatives. Hsieh et al. fail, however, to teach each and every element of the

presently claimed composition, and furthermore Hsieh et al. are silent with respect to maintaining stem cell pluripotency without differentiating the stem cell. Accordingly, it is respectfully submitted that the present rejection under §102 over Hsieh et al. has been overcome and should be withdrawn.

REJECTIONS UNDER 35 U.S.C. §103

The PTO rejects claim 11 under 35 U.S.C. §103 for alleged obviousness over Hsieh et al. (1999 *Nature* 398:431-436, of record) in view of Racher et al. (1995 *Biotechnol. Techniques* 9:169-174). More specifically, the PTO asserts that Hsieh et al. teach cell line HEK293-conditioned serum-free medium that contains a WIF-1 polypeptide comprising the sequence set forth in SEQ ID NO:4 of the present application, and that Racher et al. teach serum free medium containing glucose as supporting 293 cell survival. The Examiner alleges that the skilled artisan would reasonably conclude that "stem cell survival agents", including glucose and other media components that are "essential for the survival of any cell, including stem cells, are within the scope of 'stem cell survival agents' ".

Applicants respectfully traverse these grounds for rejection and submit that the rejection has been obviated by cancellation of claim 11 without prejudice according to the amendment submitted herewith. Additionally, and with regard to the presently amended claims, applicants submit that the encompassed subject matter clearly satisfies the requirements of 35 U.S.C. §103 even over Hsieh et al. in view of Racher et al.

The presently claimed embodiments relate in pertinent part to a composition for maintaining pluripotency without differentiating a stem cell, comprising an isolated polypeptide having a WIF domain and an EGF-like repeat; and an isolated stem cell survival agent that is selected from stem cell factor (SCF), Flt-3 ligand (FL) and thrombopoietin (TPO). The subject matter of the present claims is clearly distinguishable over Hsieh et al. in view of Racher et al., where the cited documents fail to teach or in any way suggest the recited combination, and in particular where neither the cited documents nor any other knowledge in the art at the time of filing the present application would have motivated the skilled person to combine an isolated

stem cell survival agent selected from SCF, FL and TPO, with a WIF domain/EGF-like repeat polypeptide, to maintain stem cell pluripotency without differentiation.

The present application thus discloses the recited combination for the first time, to arrive at a composition for maintaining stem cell pluripotency without stem cell differentiation. Insofar as Hsieh et al. and Racher et al. are silent with regard to maintaining stem cell pluripotency, and are also deficient because they fail in any way to suggest the stem cell survival agents SCF, FL and TPO, these documents as cited by the PTO are inapposite to the present claims. Moreover, the United States Supreme Court recently noted that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___ (April 30, 2007, No. 04-1350). Therefore, even where SCF, FL and TPO are known stem cell survival agents, that fact falls far short of suggesting the presently claimed combination.

Accordingly, applicants submit that prior to the instant application, the effects of the presently claimed subject matter could not have been predicted, whether in view of Hsieh et al. and Racher et al. or any other knowledge in the art at the time of filing. Specifically, the person having ordinary skill in the art could not, with the requisite reasonable expectation of success, have arrived at the present compositions for maintaining pluripotency without differentiating a stem cell (*e.g.*, specification at page 29, line 27 through page 30, line 2). As also described in the specification, for instance at pages 92-94 (including Tables 3 and 4), the stem cell survival agent stem cell factor (SCF), alone or in combination with the stem cell survival agent TPO, was incapable of maintaining significant hematopoietic stem cell populations. By contrast, the combination of SCF with WIF-1 polypeptide, or the combination of SCF and TPO with WIF-1, significantly supported the maintenance of such stem cells. It is therefore respectfully submitted that absent the disclosure of the present application, the prior art fails to provide any teaching or suggestion to combine SCF, FL and/or TPO with a WIF domain/EGF-like repeat polypeptide for any reason, much less to maintain stem cell pluripotency without differentiation.

Applicants therefore respectfully submit that the application fully complies with the requirements of 35 U.S.C. §103, such that withdrawal of the rejection is requested.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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